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Declarations under Rule 4.17:

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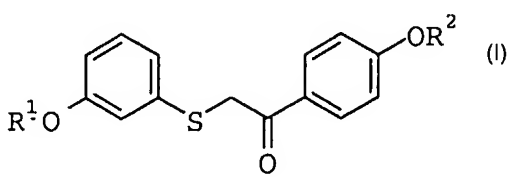
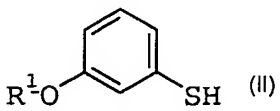
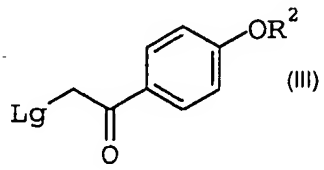
(54) Title: PROCESS FOR PREPARING $G(A)-(3-ARYLTHIO)-ACETOPHENONES



(I)



(II)



(III)

(57) Abstract: The present invention relates to a biphasic process for preparing a compound of formula (I) from a compound a compound of formula (II) and (III).

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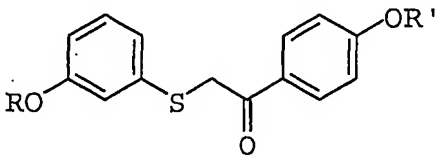
PROCESS FOR PREPARING α-(3-ARYLTHIO)-ACETOPHENONES

BACKGROUND OF THE INVENTION

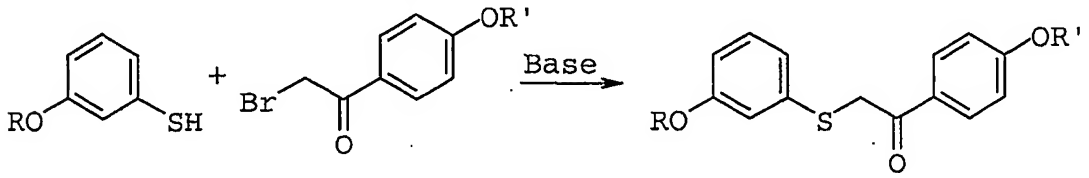
Compounds of the formula:



;

wherein R and R' are the same or different hydroxy protecting group; are intermediates to pharmaceutically active compounds (see, *e.g.*, U.S. Patent No.'s 4,075,227, 4,133,814, 4,418,068, 5,552,401 and 5,723,474).

According to the procedures described in the above mentioned patents, these intermediates are constructed via the following coupling reaction:

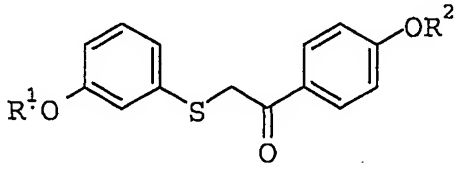


wherein the reaction is performed neat in, *e.g.*, pyridine or is performed in the presence of aqueous ethanolic potassium hydroxide. In either case, said reactions are performed in a homogenous aqueous miscible environment.

When produced by this procedure, purification of the compound of formula I would typically involve the addition of an organic solvent (aqueous immiscible) to facilitate separation of the product (which is soluble in the organic layer) from the inorganic aqueous soluble impurities. The aqueous layer would typically be removed followed by one or more aqueous acidic and basic extractions of the organic layer to remove residual base and inorganic salts.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a process for preparing a compound of formula I:

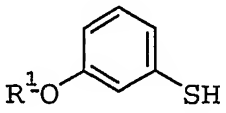


I;

wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and a hydroxy protecting group;

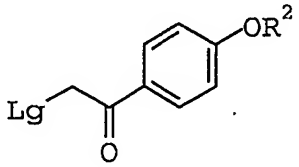
which includes reacting a compound of formula II:



II;

dissolved in a suitable alkaline aqueous solvent;

with a compound of formula III:



III

wherein Lg is a leaving group;

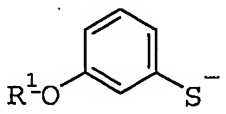
dissolved in a suitable aqueous immiscible solvent.

DETAILED DESCRIPTION OF THE INVENTION

General terms used in the description of chemical formulas bear their usual meanings. For example, the term "hydroxy protecting group" denotes a group understood by one skilled in the organic chemical arts of the type described in Chapter 2 of "Protective Groups in Organic Synthesis, 2nd Edition, T. H. Greene, *et al.*, John Wiley & Sons, New York, 1991, hereafter "Greene".

Representative hydroxy protecting groups include, for example, C_1-C_6 alkyl and substituted C_1-C_6 alkyl, including methyl, ethyl, isopropyl, cyclopropyl, methoxymethyl, methylthiomethyl, *tert*-buylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxy-benzyloxymethyl, *tert*-butoxy-methyl; ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2,2,2-trichloroethoxymethyl, and 2-(trimethylsilyl)ethyl; phenyl and substituted phenyl groups such as *p*-chlorophenyl, *p*-methoxyphenyl, and 2,4-dinitrophenyl; benzyl groups; alkylsilyl groups such as trimethyl- triethyl- and triisopropylsilyl; mixed alkylsilyl groups such as dimethylisopropylsilyl, and diethylisopropylsilyl; acyl protecting groups such as those of the general formula COC_1-C_6 alkyl or COAr; and esters of the general formula CO_2C_1-C_6 alkyl, or CO_2Ar, where Ar is phenyl or substituted phenyl as described above.

The term "leaving group" refers to an atom, or group of atoms that in the aggregate are susceptible to nucleophilic displacement by a thiolate anion, more specifically, to the thiolate shown below:



Examples of such leaving groups include halides such as Cl, Br and I; sulfonates (a group of the general formula OSO_2R^3 where R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted phenyl) such as methanesulfonate or toluenesulfonate; and phosphonates (a group of the general formula OPO_2R^3) such as methyl phosphate, ethyl phosphate or phenyl phosphate.

The term "suitable alkaline aqueous solvent" refers to a suitable base dissolved in water wherein the resulting mixture sufficiently solubilizes the compound of formula II to afford a medium within which to effect the desired

reactions are run. Therefore, the progress of the reactions should be monitored via conventional techniques, *e.g.*, HPLC, to determine when the reactions are substantially complete. Monitoring the progress of chemical reactions is well within the ordinarily skilled artisan's capability.

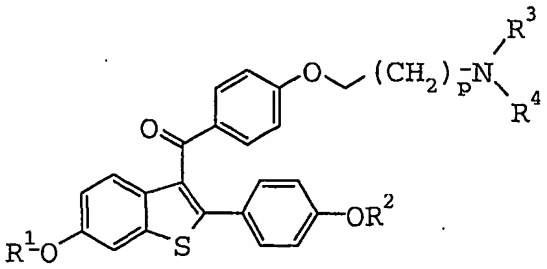
Preferred compounds of formula II for use in the present process are those where R^1 is hydrogen, methyl, isopropyl or benzyl, particularly hydrogen, methyl or benzyl. Preferred compounds of formula III for use in the present process are those where R^2 is hydrogen, methyl, isopropyl or benzyl, particularly methyl. Thus, preferred products of the above reaction include, but are not limited to, α-(3-hydroxyphenylthio)-4-methoxyacetophenone, α-(3-methoxyphenylthio)-4-methoxyacetophenone, α-(3-isopropoxyphenylthio)-4-methoxyacetophenone, and α-(3-benzyloxyphenylthio)-4-methoxyacetophenone.

As stated above, the process of the present invention is performed in a biphasic reaction medium. In general, biphasic reactions are expected to proceed at a diminished rate, relative to the corresponding mono-phasic reaction. However, biphasic reactions can offer an advantage with product purification. That is, purification is sometimes much simpler and efficient with a biphasic reaction when the product is mostly soluble in one phase and the impurities are mostly soluble in the other. To overcome reaction rate liabilities, phase transfer catalysts are typically employed in biphasic systems. Surprisingly, the present process proceeds at rates and in yields comparable to the prior art mono-phasic rates even in the absence of a phase transfer catalyst.

Furthermore, when R^1 is hydrogen in the compound of formula II, *i.e.*, when the compound of formula II is unprotected, Applicants have found that the present process proceeds without significant undesired "O-alkylation". This

surprising characteristic of the present process enables the direct synthesis of a compound of formula I where one of R^1 or R^2 is hydrogen.

In a preferred embodiment, a compound of formula I is cyclized, acylated, optionally deprotected and optionally salified to form a compound of formula IV:



IV

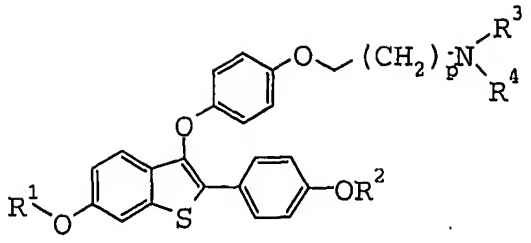
or a pharmaceutical salt thereof; wherein:

p is 0, 1 or 2; and

R^3 and R^4 are independently C_1-C_4 alkyl, or combine together with the nitrogen to which they are attached to form a piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino ring.

The cyclization, acylation and optional deprotection and salification reactions may be performed essentially as described in U.S. Patent No.'s 4,380,635, 4,418,068, 5,512,684, 5,523,416, 5,629,425, 5,731,327, 5,969,157 and 5,977,383 the teachings of each are herein incorporated by reference. The hydrochloride salt of a compound of formula IV where R^1 and R^2 is hydrogen and R^3 and R^4 combine to form a piperidinyl ring is a preferred product.

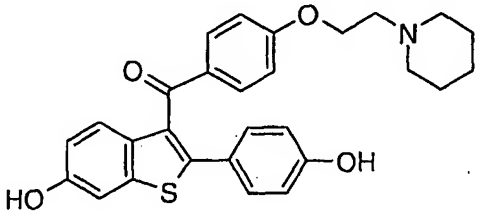
In another preferred embodiment, a compound of formula I may be cyclized, 3-halogenated, S-oxidized, have the 3-halo group displaced, reduced, optionally deprotected, and optionally salified to prepare a compound of formula V:



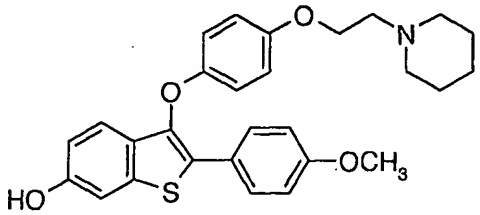
V;

or pharmaceutical salt thereof.

In a particularly preferred embodiment, a compound of formula I may be used to prepare a compound of formula VII and VIII:

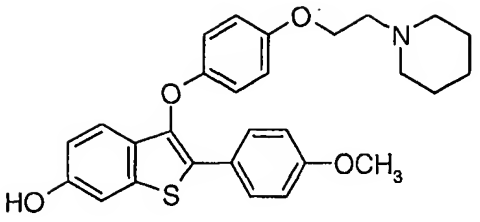


VII



VIII.

The cyclization, 3-halogenation, oxidation, nucleophilic displacement of halo, reduction, and optional deprotection and salification reactions may be performed essentially as described in U.S. Serial No. 09/XXX,XXX (Attorney Docket No. X-14146) filed on the same day as X-14145; U.S. Patent No.'s 5,510,357, 5,512,684, 5,523,416, 5,723,474, 5,969,157 and 5,977,383; and PCT Publication No.'s WO 01/09115 and WO 01/09116, the teachings of each are herein incorporated by reference. The hydrochloride salt of compound of formula V where R^1 is hydrogen, R^2 is methyl, and R^3 and R^4 combine to form piperidinyl is preferred.



VIII

or a pharmaceutically acceptable salt thereof.